PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/00, 31/195

A3

(11) International Publication Number: WO 96/02240

(43) International Publication Date: 1 February 1996 (01.02.96)

(21) International Application Number: PCT/EP95/02693

(22) International Filing Date: 7 July 1995 (07.07.95)

(30) Priority Data:
9414157.9 13 July 1994 (13.07.94) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CHRISTIE, Gary [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). WESTON, Beverley, Jane [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(88) Date of publication of the international search report:
13 February 1997 (13.02.97)

(54) Title: USE OF INHIBITORS OF HUMAN S-CD23

(57) Abstract

Inhibitors of matrix metalloproteases such as collagenase are capable of inhibiting the release of human soluble CD23 and are therefore useful in the treatment and prophylaxis of conditions in which an excess of s-CD23 is implicated, such as allergy and autoimmune disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

In' tional Application No
PCT/EP 95/02693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 447 353 (CIBA-GEIGY AG) 18 September 1991 see the whole document ---	1-10
X	WO,A,94 10990 (BRITISH BIO-TECHNOLOGY LIMITED) 26 May 1994 see the whole document ---	1-10
X	WO,A,93 20047 (BRITISH BIO-TECHNOLOGY LIMITED) 14 October 1993 see the whole document ---	1-10
X	WO,A,90 11287 (UNITED STATES OF AMERICA) 4 October 1990 see the whole document ---	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 1996	16.01.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In' tional Application No
PCT/EP 95/02693

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 05719 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 see page 22 - page 25	5-10
X	WO,A,90 05716 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 see page 28 - page 30	5-10
X	J.CLIN.INVEST., vol. 94, no. 6, 1994 pages 2177-2182, K.GIJBELS ET AL. 'Reversal of Experimental Autoimmune Encephalomyelitis with a Hydroxamate Inhibitor of Matrix Metalloproteases' see the whole document	1-10
X,P	INFLAMMATION RESEARCH, vol. 44, no. 8, 1995 pages 345-349, A.K.HEWSON ET AL. 'Suppression of experimental allergic encephalomyelitis in the Lewis rat by the matrix metalloproteinase inhibitor Ro31-9790' see abstract	1-10
X,P	WO,A,94 21625 (BRITISH BIOTECHNOLOGY LIMITED) 29 September 1994 see page 1	1
X,P	WO,A,94 24140 (BRITISH BIO-TECHNOLOGY LIMITED) 27 October 1994 see page 1	1
X	WO,A,93 18173 (XENOVA LIMITED) 16 September 1993 see page 1	1-10
X	WO,A,92 16517 (XENOVA LIMITED) 1 October 1992 see page 1	1-10
A	WO,A,92 05447 (THE SALK INSTITUTE FOR BIOLOGICAL STUDIES) 2 April 1992 see page 1	1
X,P	WO,A,95 09841 (BRITISH BIO-TECHNOLOGY LIMITED) 13 April 1995 see page 1	1
2 X,P	WO,A,95 13289 (CHIROSCIENCE LIMITED) 18 May 1995 see page 1	1

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 95/02693

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO,A,95 19961 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1	1
E	WO,A,95 19957 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1	1
E	WO,A,95 19956 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1	1
A	NATURE, vol. 366, 2 December 1993 pages 421-428, B.J.SUTTON ET AL. 'The human IgE network' cited in the application see the whole document	1-10
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 93-375338 & KR,A,9 302 833 (KOREA ADV INST SCI & TECHN) , 10 April 1993 see abstract	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

..ternational application No.
PCT/EP 95/02693

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 4,9 and 10 are directed to a method of treatment of the human/animal body the search has been based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see additional sheet!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP95/02693

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

INCOMPLETE SEARCH

2. Obscurities,...etc.

The expressions "an inhibitor of the formation of human soluble CD23 (S-CD23)" and "an inhibitor of a matrix metalloprotease" are not proper definitions of chemical compounds in structural terms. The expression "disorders in which the overproduction of S-CD23 is implicated" is not a proper definition of a therapeutic application.

The references to the description in claims 9 and 10 do not meet the requirements of Rule 6.2(a)PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 95/02693

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0447353	18-09-91	AT-T-	109005	15-08-94
		AU-B-	643245	11-11-93
		AU-B-	6934791	25-07-91
		DE-D-	69103053	01-09-94
		DE-T-	69103053	01-12-94
		ES-T-	2057833	16-10-94
		JP-A-	5117163	14-05-93
		US-A-	5236706	17-08-93
WO-A-9410990	26-05-94	AU-B-	5430194	08-06-94
		EP-A-	0667770	23-08-95
WO-A-9320047	14-10-93	AU-B-	3899193	08-11-93
		EP-A-	0634998	25-01-95
		JP-T-	7505387	15-06-95
		ZA-A-	9302501	08-11-93
WO-A-9011287	04-10-90	AU-B-	634533	25-02-93
		AU-B-	5359190	22-10-90
		CA-A-	2046649	22-09-90
		EP-A-	0464147	08-01-92
		JP-T-	4504418	06-08-92
WO-A-9005719	31-05-90	AU-B-	644064	02-12-93
		AU-B-	4800390	12-06-90
		DE-D-	68914687	19-05-94
		DE-T-	68914687	08-09-94
		EP-A-	0446267	18-09-91
		ES-T-	2055409	16-08-94
		JP-T-	4502008	09-04-92
		NO-B-	177701	31-07-95
		US-A-	5310763	10-05-94
		US-A-	5240958	31-08-93
WO-A-9005716	31-05-90	AU-B-	641629	30-09-93
		AU-B-	4746890	12-06-90
		DE-D-	68913988	21-04-94
		DE-T-	68913988	28-07-94
		EP-A-	0445206	11-09-91
		ES-T-	2063334	01-01-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

In' tional Application No
PCT/EP 95/02693

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9005716		JP-T-	4503057	04-06-92
		NO-B-	177700	31-07-95
		US-A-	5304604	19-04-94
WO-A-9421625	29-09-94	AU-B-	6213194	11-10-94
		EP-A-	0689538	03-01-96
		FI-A-	954351	15-09-95
		GB-A-	2290543	03-01-96
		NO-A-	953652	15-09-95
WO-A-9424140	27-10-94	AU-B-	6510294	08-11-94
WO-A-9318173	16-09-93	GB-A,B	2280439	01-02-95
WO-A-9216517	01-10-92	EP-A-	0580609	02-02-94
		GB-A,B	2269382	09-02-94
		JP-T-	6506202	14-07-94
WO-A-9205447	02-04-92	AU-B-	655943	19-01-95
		AU-B-	8630991	15-04-92
		EP-A-	0552202	28-07-93
		JP-T-	6503642	21-04-94
WO-A-9509841	13-04-95	AU-B-	7787594	01-05-95
WO-A-9513289	18-05-95	AU-B-	8113394	29-05-95
WO-A-9519961	27-07-95	AU-B-	1460395	08-08-95
WO-A-9519957	27-07-95	NONE		
WO-A-9519956	27-07-95	AU-B-	1459795	08-08-95

PCT WORLD INTELLE

INTERNATIONAL APPLICATION PUBLISH

(51) International Patent Classification 6 :
A61K 31/00, 31/195

A2

(43) International Publication Date: 1 February 1996 (01.02.96)

(21) International Application Number: PCT/EP95/02693

(22) International Filing Date: 7 July 1995 (07.07.95)

(30) Priority Data:
9414157.9 13 July 1994 (13.07.94) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHRISTIE, Gary [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). WESTON, Beverley, Jane [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: USE OF INHIBITORS OF HUMAN S-CD23

(57) Abstract

Inhibitors of matrix metalloproteases such as collagenase are capable of inhibiting the release of human soluble CD23 and are therefore useful in the treatment and prophylaxis of conditions in which an excess of s-CD23 is implicated, such as allergy and autoimmune disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

USE OF INHIBITORS OF HUMAN S-CD23

This invention relates to a medical use and in particular to the use of inhibitors of the formation of soluble human CD23 for the treatment of conditions associated with excess production of soluble CD23 (s-CD23) such as autoimmune disease and allergy.

Matrix metalloproteases such as collagenase, stromelysin and gelatinase are known to be involved in connective tissue breakdown. Known classes of matrix metalloprotease inhibitors include derivatives of hydroxamic acid, phosphonates and thiols.

International Patent Application, Publication Number WO 93/20047 discloses that inhibitors of the matrix metalloproteases, especially derivatives of hydroxamic acid, are potentially useful for the treatment or prophylaxis of conditions involving such tissue breakdown, for example rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration, and tumour metastasis or invasion.

WO 93/20047 discloses various derivatives of hydroxamic acid including those from the following patent publications: USP 4599361, EP-A-0236872, EP-A-0274453, WO 90/05716, WO 90/05719, WO 91/02716, EP-A-0489577, EP-A-0489579, EP-A-0497192 and WO 92/13831.

CD23 (the low affinity IgE receptor FcεRII, Blast 2), is a 45 kDa type II integral protein expressed on the surface of a variety of mature cells, including B and T lymphocytes, macrophages, natural killer cells, Langerhans cells, monocytes and platelets (Delespesse *et al, Adv Immunol*, 49 [1991] 149-191). There is also a CD23-like molecule on eosinophils (Grangette *et al, J Immunol*, 143 [1989] 3580-3588). CD23 has been implicated in the regulation of the immune response (Delespesse *et al, Immunol Rev*, 125 [1992] 77-97). Human CD23 exists as two differentially regulated isoforms, a and b, which differ only in the amino acids at the intracellular N-terminus (Yokota *et al, Cell*, 55 [1988] 611-618). In man the a isoform is found only on B-lymphocytes, whereas type b is found on all other cells capable of expressing CD23. However, expression of the b isoform on B-lymphocytes is inducible by IL4. Intact, cell bound CD23 (i-CD23) is known to undergo cleavage from the cell surface leading to the formation of a number of well-defined soluble fragments (s-CD23), which are produced as a result of a complex sequence of proteolytic events, the mechanism of which is still poorly understood (Bourget *et al J Biol Chem*, 269 [1994] 6927-6930). Although not yet proven, it is postulated that the major soluble fragments (Mr 37, 33, 29 and 25 kDa) of these proteolytic events, all of which retain the C-terminal lectin domain common to i-CD23, occur sequentially via initial formation of the 37 kDa fragment (Letellier *et al, J Exp Med*, 172 [1990] 693-700).

An alternative intracellular cleavage pathway leads to a stable 16 kDa fragment differing in the C-terminal domain from i-CD23 (Grenier-Brosette *et al, Eur J Immunol*, 22 [1992] 1573-1577).

Several activities have been ascribed to membrane bound i-CD23 in humans, all of which have been shown to play a role in IgE regulation. Particular activities include: a) antigen presentation, b) IgE mediated eosinophil cytotoxicity, c) B cell homing to germinal centres of lymph nodes and spleen, and d) downregulation of IgE synthesis (Delespesse *et al, Adv Immunol*, 49, [1991] 149-191). The three higher molecular weight soluble CD23 fragments (Mr 37, 33 and 29 kDa) have multifunctional cytokine properties which appear to play a major role in IgE production. Thus, the excessive formation of s-CD23 has been implicated in the overproduction of IgE, the hallmark of allergic diseases such as extrinsic asthma, rhinitis, allergic conjuctivitis, eczema, atopic dermatitis and anaphylaxis (Sutton and Gould, *Nature*, 366, [1993] 421-428). Other biological activities attributed to s-CD23 include the stimulation of B cell growth and the induction of the release of mediators from monocytes. Thus, elevated levels of s-CD23 have been observed in the serum of patients having B-chronic lymphocytic leukaemia (Sarfati *et al, Blood*, 71 [1988] 94-98) and in the synovial fluids of patients with rheumatoid arthritis (Chomarat *et al, Arthritis and Rheumatism*, 36 [1993] 234-242).

Because of these various properties of CD23, compounds which inhibit the formation of s-CD23 should have twofold actions of a) enhancing negative feedback inhibition of IgE synthesis by maintaining levels of i-CD23 on the surface of B cells, and b) inhibiting the immunostimulatory cytokine activities of higher molecular weight soluble fragments (Mr 37, 33 and 29 kDa) of s-CD23.

It has now surprisingly been found that compounds which inhibit the action of matrix metalloproteases (eg collagenase, stromelysin and gelatinase) are effective inhibitors of the release of human soluble CD23 transfected into mammalian cell culture systems. It is also indicated that such compounds inhibit the formation of IgE by human peripheral blood mononuclear cells in response to IL4 and stimulation with an antibody to CD40. Inhibitors of the matrix metalloproteases are therefore potentially useful for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of s-CD23 is implicated. Known classes of matrix metalloprotease inhibitors include derivatives of hydroxamic acid, phosphonic acid and thiols, all of which have been shown to inhibit CD23 proteolysis.

Accordingly, the present invention provides the use of an inhibitor of the formation of human soluble CD23, such as an inhibitor of matrix metalloproteases, for the production of a medicament for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of s-CD23 is implicated.

In a further aspect the invention provides a method for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of s-CD23 is implicated, which method comprises the administration of an inhibitor of the formation of soluble human CD23, such as an inhibitor of matrix metalloproteases, to a human or non-human mammal in need thereof.

The invention also provides a pharmaceutical composition for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of s-CD23 is implicated which comprises an inhibitor of the formation of soluble human CD23, such as an inhibitor of matrix metalloproteases and optionally a pharmaceutically acceptable carrier therefor.

Suitable matrix metalloprotease inhibitors are set out in the Table and include the hydroxamic acid derivatives disclosed in WO 90/05716, WO 90/05719, WO 91/02716, WO 92/13831, WO 93/20047, EP-A-0236872, EP-A-0274453, EP-A-0489577, EP-A-0489579, EP-A-0497192 and USP 4599361.

Suitable matrix metalloprotease inhibitors also include the thiols and phosphonic acids disclosed in EP 273689 and EP320118.

The contents of WO 90/05716, WO 90/05719, WO 91/02716, WO 92/13831, WO 93/20047, EP-A-0236872, EP-A-0274453, EP-A-0489577, EP-A-0489579, EP-A-0497192, USP 4599361, EP 273689 and EP320118, and the other patent publications referred to in the Table, are incorporated herein by reference, including the specific examples disclosed in these patent publications.

Particular matrix metalloprotease inhibitors include the compounds disclosed hereinafter in the Procedures section.

Favoured matrix metalloprotease inhibitors include Example 2 of WO 90/05719 and Example 1 of EP 0497192.

It is to be understood that the pharmaceutically acceptable salts, solvates and other pharmaceutically acceptable derivatives of the above mentioned matrix metalloproteases inhibitors are also included in the present invention.

The matrix metalloprotease inhibitors mentioned herein may exist in several different isomeric forms, including stereoisomeric forms. Unless specifically stated to the contrary herein with respect to particular compounds, all isomers including stereoisomers and mixtures of isomers, such as racemic mixtures, are included within the present invention.

The matrix metalloprotease inhibitors of the invention may be prepared by use of any approriate conventional method, for example the matrix metalloprotease inhibitors disclosed in patent publications WO 90/05716, WO 90/05719, WO 91/02716, WO 92/13831, WO 93/20047, EP-A-0236872, EP-A-0274453, EP-A-0489577, EP-A-0489579, EP-A-0497192 and USP 4599361, EP 273689 and EP320118 may be prepared by the methods disclosed therein.

The isomers, including stereoisomers, of the matrix metalloprotease inhibitors of the present invention may be prepared as mixtures of such isomers or as individual isomers. The individual isomers may be prepared by any appropriate method, for example individual stereoisomers may be prepared by stereospecific chemical synthesis starting from chiral substrates or by separating mixtures of enantiomers using known methods.

It is preferred that the matrix metalloprotease inhibitors are isolated in substantially pure form.

As used herein the term "matrix metalloprotease inhibitor" and equivalent terms means any compound which inhibits any member of the family of zinc and calcium dependent endopeptidases (matrix metalloproteases) that have the ability to degrade components of the connective tissue matrices. Matrix metalloproteases and their inhibition are discussed by *inter alia* Hooper, FEBS Letters 1994, 354,1-6; Gordon et al., Clinical and Experimental Rheumatology 1993, 11(Suppl. 8), S91-S94; Woessner, FASEB 1991, 5, 2145-2154; and Birkedal-Hansen, Critical Reviews in Oral Biology and Medicine 1993, 4(2), 197-250. Assays for inhibition of collagenase, stromelysin, and gelatinase are described in WO 90/05719, page 67, WO 90/05719, page 68, and EP-A-0 489 577, pages 25-26, respectively. The present invention comprehends the use of compounds which are deemed active in any one of these assays, as well as the specific compounds set out in the Table.

As stated herein an inhibitor of the formation of soluble human CD23, such as a matrix metalloprotease inhibitor, has useful medical properties. Preferably the active compounds are administered as pharmaceutically acceptable compositions.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example in the form of a spray, aerosol or other conventional method for inhalation, for treating respiratory tract disorders; or parenteral administration for patients suffering from heart failure. Other alternative modes of administration include sublingual or transdermal administration.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone;

fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions of this invention may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a

nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, preferably less than 10 microns for example diameters in the range of 1-50 microns, 1-10 microns or 1-5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; xanthine derivatives such as theophylline and aminophylline and corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending upon the method of administration. A preferred range for inhaled administration is 10-99%, especially 60-99%, for example 90, 95 or 99%.

Microfine powder formulations may suitably be administered in an aerosol as a metered dose or by means of a suitable breath-activated device.

Suitable metered dose aerosol formulations comprise conventional propellants, cosolvents, such as ethanol, surfactants such as oleyl alcohol, lubricants such as oleyl alcohol, desiccants such as calcium sulphate and density modifiers such as sodium chloride.

Suitable solutions for a nebulizer are isotonic sterilised solutions, optionally buffered, at for example between pH 4-7, containing up to 20mg/ml of compound but more generally 0.1 to 10mg/ml, for use with standard nebulisation equipment.

An effective amount will depend on the relative efficacy of the compounds of the present invention, the severity of the disorder being treated and the weight of the sufferer. Suitably, a unit dose form of a composition of the invention may contain from 0.1 to 1000mg of a compound of the invention (0.001 to 10mg via inhalation) and more usually from 1 to 500mg, for example 1 to 25 or 5 to 500mg. Such compositions may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, in a manner such that the daily dose is from 1mg to 1g for a 70 kg human adult and more particularly from 5 to 500mg. That is in the range of about 1.4×10^{-2} mg/kg/day to 14 mg/kg/day and more particularly in the range of about 7×10^{-2} mg/kg/day to 7 mg/kg/day.

TABLE

Patent publication	Compounds disclosed	Specific compounds and methods of preparation- Example Nos.
US-A-4,595,700	Compounds of formula (I) as defined in claim 1, optionally as further subdefined in the description.	1 to 8.
US-A-4,599,361		1 to 7.
GB-A-2 268 934		1 to 10.
GB-A-2 272 441		1 to 5.
EP-A-0 231 081		1 to 8.
EP-A-0 236 872		1 to 28.
EP-A-0 262 053		1 to 15.
EP-A-0 273 689		1 to 38.
EP-A-0 276 436		1 to 44.
EP-A-0 274 453		1 to 8.
EP-A-0 320 118		1 to 5.
EP-A-0 489 577		1 to 25.
EP-A-0 489 579		1 to 4.
EP-A-0 497 192		1 to 80.
EP-A-0 498 665		1 to 27.
EP-A-0 520 573		1 to 34.
EP-A-0 574 758		1 to 43.
EP-A-0 575 844		1 to 27.
EP-A-0 606 046		1 to 32.
EP-A-0 613 883		1 to 7.
EP-A-0 621 270		1 to 40.
WO 90/05716		1 to 38.
WO 90/05719		1 to 26.
WO 91/02716		1 to 17.
WO 92/09563	Compounds of formula (1) or (2) as defined in claim 1, optionally as further subdefined in the description.	1 to 21.

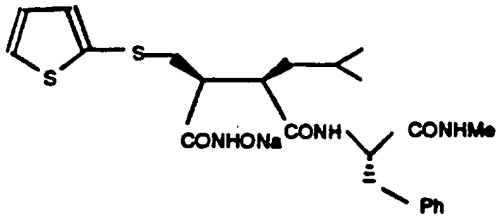
TABLE contd.

Patent publication	Compounds disclosed	Specific compounds and methods of preparation- Example Nos.
WO 92/13831	Compounds of formula (I) as defined in claim 1, optionally as further subdefined in the description.	1 to 27.
WO 92/21360		1 to 5.
WO 92/22523		I to X.
WO 93/14096		1 to 8.
WO 93/20047		1 to 14.
WO 93/24475		1 to 6.
WO 93/24449		1 to 8.
WO 94/00119		1 to 86.
WO 94/07481		1 to 15.
WO 94/12169		1 to 24.
WO 94/21625		1 to 7.
WO 94/21612		1 to 116.
WO 94/24140		1 to 5.
WO 94/25434		1 to 7.
WO 94/25435		Example 1.
WO 95/04033		Examples 1 to 7.
WO 95/04715		All examples.
WO 95/12603		All examples.

The following examples illustrate the invention but do not limit it in any way.

Preparations:

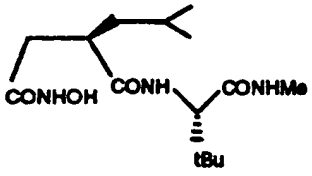
Preparation 1: [4-(N-Hydroxyamino)-2-(R)-isobutyl-3-(S)-(2-thiophenethiomethyl)succinyl]-(S)-phenylalanine-N-methylamide, sodium salt



(P1)

This is prepared according to the procedure disclosed in WO 90/05719 (see example 11, the free acid being prepared in example 2).

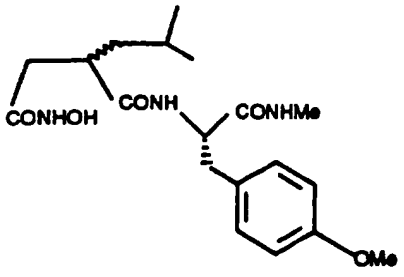
Preparation 2: (R)-[Hydroxycarbamoylmethyl]-4-methylvaleryl]-N^1, 3-dimethyl-(S)-valinamide.



(P2)

This is prepared according to the procedure disclosed in EP 0497192 (see example 1).

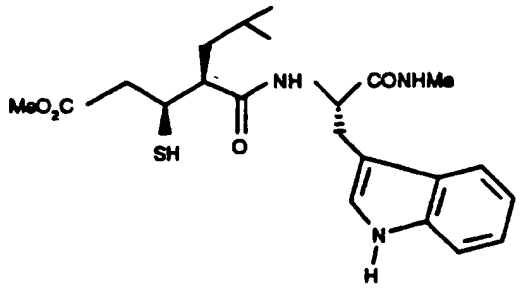
Preparation 3: N-[3-(N'-Hydroxycarboxamido)-2-(2-methylpropyl)-propanoyl-(S)-O-methyl-L-tyrosine-N-methylamide



(P3)

This is prepared according to the procedure disclosed in USP 4599361 (see example 1).

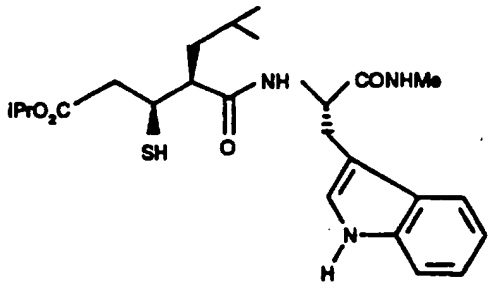
Preparation 4: Methyl 3-(S)-mercapto-6-methyl-4-(S)-[[[1(S)-[(methylamino)carbonyl]-2-(3-indolyl)ethyl]amino]carbonyl]heptanoate



(P4)

This is prepared according to the procedure disclosed in EP 273689 and J. Medicinal Chemistry 1993, 36, 4030-40 (see compound 56).

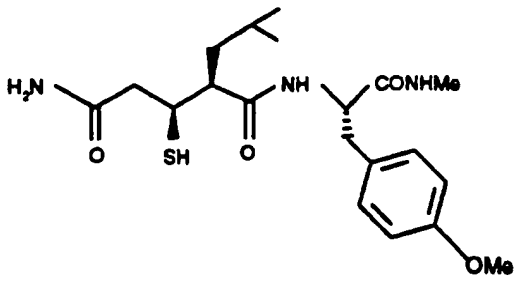
Preparation 5: Isopropyl 3-(S)-mercapto-6-methyl-4-(S)-[[[1(S)-[(methylamino)carbonyl]-2-(3-indolyl)ethyl]amino]carbonyl]heptanoate



(P5)

This is prepared according to the procedures disclosed in EP 273689.

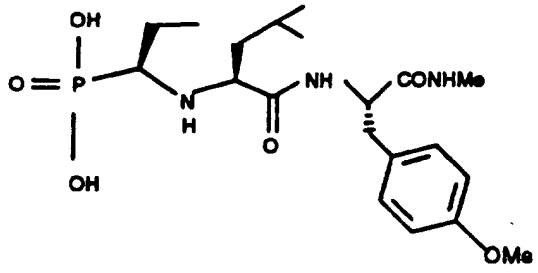
Preparation 6: 3-(S)-Mercapto-$\underline{N}^1$-[1-(S)-[methylamino)carbonyl]-2-(4-methoxyphenyl)ethyl]-2-(S)-(2-methylpropyl)pentanediamide



(P6)

This is prepared according to the procedure disclosed in J. Medicinal Chemistry *ibidem* (see compound 47a).

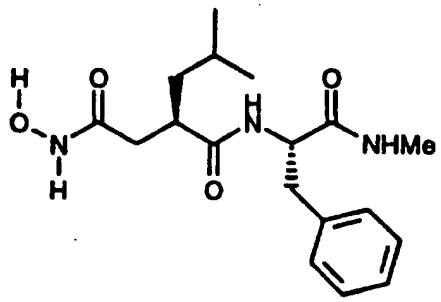
Preparation 7: N-[N-((S)-1-Phosphonopropyl)-(S)-leucyl]-O-methyl-(S)-tyrosine N-methylamide



(P7)

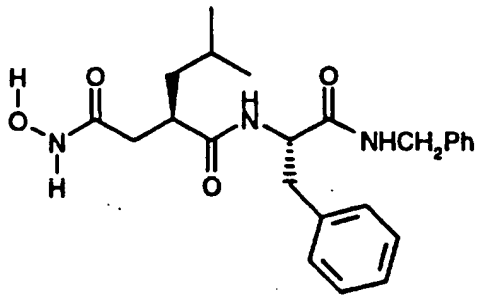
This is prepared according to the procedure disclosed in EP 320118 and J. Medicinal Chemistry 1994, 37, 158-169 (see compound 12).

Preparation 8: N-[3-(Hydroxycarboxamido)-2R-(2-methylpropyl)propanoyl-(S)-phenylalanine-N-methylamide



This is prepared by hydrogenolysis (using $Pd/BaSO_4$ as catalyst) of the precursor benzhydroxamate, itself prepared from the analogous carboxylic acid and O-benzylhydroxylamine using similar methodology to that described in WO 90/05719 example 1g

Preparation 9: N-[3-(Hydroxycarboxamido)-2R-(2-methylpropyl)propanoyl-(S)-phenylalanine-N-benzylamide



This is prepared from the precursor carboxylic acid and O-trimethylsilylhydroxylamine using similar methodology to that described in WO 90/05719 example 1g but with bromo-tris-pyrrolidino-phosphonium hexafluorophosphate replacing water soluble carbodiimide as coupling agent.

BIOLOGICAL TEST METHODS

Procedure 1: The ability of test compounds to inhibit the release of soluble CD23 was investigated by use of the following procedure.

Adherent Chinese Hamster Ovary cells which had been transfected with the alpha form of CD23 were grown in microtitre plates. Cells were grown to confluence in α-MEM medium with 10% foetal calf serum, 2mM glutamine containing 800 micro g/ml G418. Medium was removed and the cells washed with sterile phosphate buffered saline. Test compounds were dissolved in dimethyl sulphoxide at a stock concentration of 20mM, then diluted 1 in 200 with α-MEM containing 800 micro g/ml G418 (no foetal calf serum). 100ml of the diluted compounds were added to the adherent cells in triplicate wells. Appropriate control cultures were set up in triplicate. The plates were incubated for 6 hours at 37°C, 95% air/5% CO_2 in a humidified incubator, then centrifuged at 200x g for 3 minutes. A specific ELISA for CD23, obtained from The Binding Site Limited, Institute of Research and Development, Birmingham England, was used to measure CD23 levels in the culture supernatants.

The average concentration (IC_{50}) of test compound which inhibits the release of soluble CD23 by 50% relative to the control culture was determined.

Results

Test Compound No.	IC_{50} (microM)
P1	0.05
P2	0.05
P3	3.35
P4	2.2
P5	60
P6	60
P7	30

Procedure 2:

The ability of test compounds to inhibit the formation of human IgE *in vitro* was investigated using the following procedure:

Human peripheral blood mononuclear cells were separated by centrifugation over Ficoll-Paque (Pharmacia). The cells were suspended in RPMI 1640 medium containing 10% foetal calf serum, 2mM glutamine, 50 microM 2-mercaptoethanol and 50 micro g/ml gentamycin (TCM) at a concentration of 1.25 x 10^6 cells/ml. 800 micro l of the cell suspension were aliquoted into the wells of a 48 well plate. 100 micro l of TCM or IL4 at 500ng/ml was added in quadriplicate to the appropriate wells, followed by 100 micro l of TCM or 10x the final concentration of compound under investigation. Test compounds are dissolved in dimethylsulphoxide (DMSO) at a stock dilution of 10^{-2}M diluted 1 in 100 in TCM and then as above. The plates are incubated for 12 days at 37°C in a 95% air/5% CO_2 humidified incubator. At the end of the culture period the supernatants were removed with the wells and centrifuged (200xg for 10 minutes) to remove any non-adherent cells. There was no toxicity as assessed by trypan blue dye exclusion. The IgE concentration in the supernatants was measured by ELISA.

Results

		IgE ng/ml (mean +/-sem)
TCM		0.25+/-0.08
IL4 (5ng/ml)		72.4
IL4 with P1:	10^{-5}M	3.2+/-1.9
	10^{-6}M	21.3+/-16.5
	10^{-7}M	68.8+/-21.8

Procedure 3

The ability of test compounds to inhibit the formation of human IgE *in vitro* was investigated using the following procedure:

Human tonsillar B lymphocytes were suspended in RPMI 1640 medium containing 10% foetal calf serum, 2mM glutamine, 50 micro M 2-mercaptoethanol and 50 micro g/ml gentamycin (TCM) at a concentration of 1.25 x 10^6 cells/ml. 800 micro l of the cell suspension were aliquoted into the wells of a 48 well plate. 100 micro l of TCM or IL4 at 100ng/ml and antibody to CD40 at 10 microg/ml was added in quadriplicate to the appropriate wells, followed by 100 micro l of TCM or 10x the final concentration of compound under investigation. Test compounds are dissolved in DMSO at a stock dilution of 10^{-2}M diluted 1 in 100 in TCM and then as above. The plates are incubated for 11 days at 37°C in a 95% air/5% CO_2 humidified incubator. At the end of the culture period the supernatents were removed from the wells and centrifuged (200xg for 10 minutes) to remove any

non-adherent cells. There was no toxicity as assessed by trypan dye exclusion. The IgE concentration in the supernatants was measured by ELISA.

Results

		IgE ng/ml (mean +/-sem)
TCM		1.9
IL4 (10ng/ml) and anti CD40 (1 micro g/ml)		11.7+/-1.1
IL4 with P1:	10^{-5}M	2.9+/-0.2
	10^{-6}M	4.3+/-0.6
	10^{-7}M	6.2+/-0.5

Claims

1. Use of an inhibitor of the formation of human soluble CD23 (s-CD23) for the manufacture of a medicament for use in the treatment or prophylaxis of disorders in which the overproduction of s-CD23 is implicated.

2. Use according to Claim 1, wherein the inhibitor of the formation of s-CD23 is an inhibitor of a matrix metalloprotease.

3. Use according to Claim 1 or 2, for the manufacture of a medicament for use in the treatment or prophylaxis of allergy or autoimmune disease.

4 A method for the treatment or prophylaxis of disorders in which the overproduction of s-CD23 is implicated, which method comprises the administration of an effective amount of an inhibitor of the formation of human soluble CD23 to a human or non-human mammal in need thereof.

5. A pharmaceutical composition for the treatment or prophylaxis of disorders in which the overproduction of s-CD23 is implicated, which comprises an inhibitor of the formation of human soluble CD23.

6. A pharmaceutical composition according to Claim 5, further comprising a pharmaceutically acceptable carrier.

7 A pharmaceutical composition according to Claim 5 or 6, for use in the treatment or prophylaxis of allergy or autoimmune disease.

8 A pharmaceutical compostion according to any one of Claims 5 to 7, wherein the inhibitor of the formation of s-CD23 is an inhibitor of a matrix metalloprotease.

9 Use according to any one of Claims 1 to 3, a method according to Claim 4, or a pharmaceutical compostion according to any one Claims 6 to 8, substantially as hereinbefore described with reference to the Table.

10. Use according to any one of Claims 1 to 3, a method according to Claim 4, or a pharmaceutical compostion according to any one Claims 6 to 8, substantially as hereinbefore described in any one of Preparations 1 to 9.

INTERNATIONAL SEARCH REPORT

In' tional Application No
PCT/EP 95/02693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 447 353 (CIBA-GEIGY AG) 18 September 1991 see the whole document ---	1-10
X	WO,A,94 10990 (BRITISH BIO-TECHNOLOGY LIMITED) 26 May 1994 see the whole document ---	1-10
X	WO,A,93 20047 (BRITISH BIO-TECHNOLOGY LIMITED) 14 October 1993 see the whole document ---	1-10
X	WO,A,90 11287 (UNITED STATES OF AMERICA) 4 October 1990 see the whole document ---	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 January 1996	16. 01. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 05719 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 see page 22 - page 25	5-10
X	WO,A,90 05716 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 see page 28 - page 30	5-10
X	J.CLIN.INVEST., vol. 94, no. 6, 1994 pages 2177-2182, K.GIJBELS ET AL. 'Reversal of Experimental Autoimmune Encephalomyelitis with a Hydroxamate Inhibitor of Matrix Metalloproteases' see the whole document	1-10
X,P	INFLAMMATION RESEARCH, vol. 44, no. 8, 1995 pages 345-349, A.K.HEWSON ET AL. 'Suppression of experimental allergic encephalomyelitis in the Lewis rat by the matrix metalloproteinase inhibitor Ro31-9790' see abstract	1-10
X,P	WO,A,94 21625 (BRITISH BIOTECHNOLOGY LIMITED) 29 September 1994 see page 1	1
X,P	WO,A,94 24140 (BRITISH BIO-TECHNOLOGY LIMITED) 27 October 1994 see page 1	1
X	WO,A,93 18173 (XENOVA LIMITED) 16 September 1993 see page 1	1-10
X	WO,A,92 16517 (XENOVA LIMITED) 1 October 1992 see page 1	1-10
A	WO,A,92 05447 (THE SALK INSTITUTE FOR BIOLOGICAL STUDIES) 2 April 1992 see page 1	1
X,P	WO,A,95 09841 (BRITISH BIO-TECHNOLOGY LIMITED) 13 April 1995 see page 1	1
X,P	WO,A,95 13289 (CHIROSCIENCE LIMITED) 18 May 1995 see page 1	1

-/--

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 95/02693

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO,A,95 19961 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1 ---	1
E	WO,A,95 19957 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1 ---	1
E	WO,A,95 19956 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 27 July 1995 see page 1 ---	1
A	NATURE, vol. 366, 2 December 1993 pages 421-428, B.J.SUTTON ET AL. 'The human IgE network' cited in the application see the whole document ---	1-10
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 93-375338 & KR,A,9 302 833 (KOREA ADV INST SCI & TECHN) , 10 April 1993 see abstract -----	1-10

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

..ternational application No.
PCT/EP 95/02693

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 4,9 and 10 are directed to a method of treatment of the human/animal body the search has been based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see additional sheet!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP95/02693

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

INCOMPLETE SEARCH

2. Obscurities,...etc.

The expressions "an inhibitor of the formation of human soluble CD23 (S-CD23)" and "an inhibitor of a matrix metalloprotease" are not proper definitions of chemical compounds in structural terms. The expression "disorders in which the overproduction of S-CD23 is implicated" is not a proper definition of a therapeutic application.

The references to the description in claims 9 and 10 do not meet the requirements of Rule 6.2(a)PCT.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In' tional Application No
PCT/EP 95/02693

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0447353	18-09-91	AT-T-	109005	15-08-94
		AU-B-	643245	11-11-93
		AU-B-	6934791	25-07-91
		DE-D-	69103053	01-09-94
		DE-T-	69103053	01-12-94
		ES-T-	2057833	16-10-94
		JP-A-	5117163	14-05-93
		US-A-	5236706	17-08-93
WO-A-9410990	26-05-94	AU-B-	5430194	08-06-94
		EP-A-	0667770	23-08-95
WO-A-9320047	14-10-93	AU-B-	3899193	08-11-93
		EP-A-	0634998	25-01-95
		JP-T-	7505387	15-06-95
		ZA-A-	9302501	08-11-93
WO-A-9011287	04-10-90	AU-B-	634533	25-02-93
		AU-B-	5359190	22-10-90
		CA-A-	2046649	22-09-90
		EP-A-	0464147	08-01-92
		JP-T-	4504418	06-08-92
WO-A-9005719	31-05-90	AU-B-	644064	02-12-93
		AU-B-	4800390	12-06-90
		DE-D-	68914687	19-05-94
		DE-T-	68914687	08-09-94
		EP-A-	0446267	18-09-91
		ES-T-	2055409	16-08-94
		JP-T-	4502008	09-04-92
		NO-B-	177701	31-07-95
		US-A-	5310763	10-05-94
		US-A-	5240958	31-08-93
WO-A-9005716	31-05-90	AU-B-	641629	30-09-93
		AU-B-	4746890	12-06-90
		DE-D-	68913988	21-04-94
		DE-T-	68913988	28-07-94
		EP-A-	0445206	11-09-91
		ES-T-	2063334	01-01-95